



HIV/AIDS

CALL IT MOLECULAR JUJITSU. THE HUMAN IMMUNODEFICIENCY VIRUS THAT CAUSES AIDS

is a wily adversary, evolving around opponents enlisted to defeat it. But researchers at City of Hope in Duarte, Calif., led by John Zaia, M.D., intend to employ the strength of the virus against itself, the way jujitsu practitioners leverage an enemy's force to shape his downfall. • The lynchpin in this strategy is the protein CCR5, which makes a doorway HIV uses to enter an immune cell. Individuals resistant to HIV have a mutation in the CCR5 gene. German researchers "rein-vigorated the field," Zaia said, with a paper in the *New England Journal of Medicine* in 2009 about a stem cell transplant using cells from an HIV-resistant donor. The transplant not only successfully treated the patient's myeloid leukemia, but cleared his HIV as well. Since the treatment, doctors have been unable to detect any HIV in the patient using even the most sensitive tests.

Because of the odds against finding a matching donor with the CCR5 mutation for every person with HIV, the paper didn't show the way to a cure. But it did highlight the hope of stem cell transplants. Zaia will use stem cells to create HIV resistance with the help of molecular scissors—an engineered molecule called a zinc-finger nuclease, a technology developed by Richmond, Calif., company Sangamo BioSciences Inc.

Zinc "fingers" are peptides selected to bind to a specific area of DNA. The fingers grab a targeted sequence and sever it. Normally, the CCR5 protein snakes through the cell membrane in a series of hairpin curves. But cut the CCR5 gene, and the protein no longer appears on the cell surface; HIV's entryway disappears like a vanishing door in a Harry Potter novel.

To make the door fade forever, the gene must be disabled in a patient's stem cells, which will hand the mutation down to future cell generations. Animal studies show that only a fraction of the stem cells need the CCR5 mutation to create disease resistance. Whereas other genetic engineering approaches must alter great numbers of cells to create lasting change, and must keep those new cells running for a lifetime, the jujitsu nature of the zinc-finger approach means the zinc fingers must operate only briefly, mutating only a small percentage of all the stem cells.

Animal studies show HIV's killing efficiency becomes its undoing, jujitsu style. The disease attacks the unmutated cells. The survivors all carry the mutation, and the virus has no one to plunder. Viral levels fall.

Zaia says the first patients to try mutated cell transplants will be those with AIDS lymphoma who need a complete stem cell transplant to combat that cancer.

"There is a need for improved treatment of HIV/AIDS," Zaia says. "The zinc-finger technology offers real promise."

WHAT IS IT LIKE TO LIVE WITH HIV?

It was perhaps the biggest moment of Loring Leeds' life, but as he lay waiting for doctors to return his stem cells to his body, Leeds realized it was a signature moment for the crowd in the room as well. • It was 1998, and surrounding him were the doctors and scientists who had developed a treatment for non-Hodgkin lymphoma in AIDS patients—something most of the medical community at the time considered pointless and hopeless. But Leeds' stem cell treatment was even more dramatic, because some of his cells were genetically modified to express an enzyme researchers hoped would short-circuit AIDS.

"There was this deafening silence, and I realized that moment was the culmination of their life's work," Leeds said. Today, Leeds, an artist, is cancer free, and though the AIDS enzyme treatment did not work, his HIV is undetectable. The treatment he received was a precursor to the HIV work now being carried out by two CIRM disease teams.

"These people are the most dedicated, the most compassionate, the most passionate people I've ever met," Leeds said. "They are visionaries. They are the best humanity has to offer. I truly believe our best hope for better treatment, and ultimately a cure, will come from the hands and hearts and minds of these astonishing people."

"I truly believe
our best hope
for better
treatment,
and ultimately
a cure, will
come from
the hands and
hearts and
minds of these
astonishing
people."

LORING LEEDS

